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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Enteric-coated Tablets of Dextran Sulphate Ester and Method of Preparation Thereof

We, MEITO SANGYO KABUSHIKI KAISHA, duly organized and established under the law of Japan and located at No. 1, 1-chome, Kikui-dori, Nishi-ku, Nagoya, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

THIS INVENTION relates to enteric-coated tablets of water-soluble salts of dextran sulphate for oral administration, and a method of preparing them.

Water-soluble salts of dextran sulphate are known to have an anticoagulating action towards the blood. However, in clinical use it has been found necessary to administer them by intravenous or intramuscular injection because when administered orally they are inactivated in the stomach, and though various attempts have been made to overcome this problem it has previously not been found practicable to administer salts of dextran sulphate orally.

We have found that water-soluble salts of dextran sulphate are very effective in the treatment of hyperlipemia. In particular, we have found that very good results can be obtained using a water-soluble salt of dextran sulphate ester possessing together the specific conditions of an intrinsic viscosity [η] within the range 0.020 to 0.050 (in a 0.7 mol saline solution at 25° C.) and a sulphur content above 13% by weight. The intrinsic viscosity [η] is defined by the following formulae:

$$[\eta] = \lim_{C \to 0} (1n\eta r)/C$$

$$= \lim_{C \to 0} \eta sp/C$$

Wherein $\eta r = \eta/\eta o$

$$\eta sp = (\eta - \eta o)/\eta o = \eta r - 1$$

Where η = the viscosity of the solution,
ηo = the viscosity of the solvent, and
C = the concentration of g/100 m.,

the viscosity measurements being made with Ubbelohde's viscometer.

The intrinsic viscosity is determined graphically for the various concentrations by recording $(1n\eta r)/C$ and $\eta sp/C$ with respect to C.

The sulphur content of the salts of dextran sulphate is determined by the Schöniger's method. (Schöniger, W., Mikrohim Acta, 1956, page 869.) Oral application of the dextran sulphate salts for the treatment of hyperlipemia has presented similar problems as those presented by the desired oral administration of the salts for anti-coagulant purposes.

While the mechanism by which salts of dextran sulphate are decomposed or inactivated in the stomach is not fully understood, it is evident that it is not merely due to the influence of the metallic ions such as calcium and magnesium ions, alone in the gastric fluid, for the effect of the various enzymes should not be overlooked. Therefore, satisfactory results cannot be expected by means such as adding a substance such as, for example, ethylene diamine tetra-acetic acid (EDTA) in the administration of the foregoing salts of dextran sulphate. Moreover, in view of the toxicity of EDTA, its administration in large amounts over an extended period would be dangerous.

We have now found, according to the present invention that inactivation of the dextran sulphate salts in the stomach can be prevented by using the salts in the form of tablets which are coated uniformly with an enteric coating material that is insoluble

[Price 4s. 6d.]

in a simulated gastric fluid having a pH below 3.0 but dissolves or disintegrates in a simulated intestinal fluid having a pH 5.0—8.0. Accordingly, the present invention comprises a tablet of a water-soluble salt of dextran sulphate having a uniform coating of an enteric coating material, said coating being insoluble in simulated gastric fluid (as hereinbefore defined) of a pH less than 3.0 but which dissolves or disintegrates in a simulated intestinal fluid (as hereinbefore defined) of a pH from 5.0 to 8.0.

In general, it can be said that the gastric juice is strongly acidic while the intestinal fluid is alkaline. However, when closer investigation is made, the pH of gastric juice is found to be below 3.0, and it is reported that when this acid juice moves and mixes with the alkaline digestive fluid at the duodenum, its pH becomes about 3.6—6.6, and from jejunum to ileum, about 3.6—7.9; and it is only near the colon that a pH of above 7 is shown. In any event, it is certain that the gastroenteric fluid does not change abruptly from acid to alkaline. Hence, as the material to be used as the enteric soluble film, the requirement is that it be that which, on the one hand, is not subject to any changes at all in an acid medium of a pH below 3.0 or is not affected at least for 5—6 hours, while, on the other hand, it will dissolve or disintegrate as promptly as possible in a weak alkaline medium that is weakly acid or of a pH about 7.9. Moreover, it is demanded that it be not affected by the peptic enzymes in the gastric juice and does not possess resistance to the constituents of the intestinal fluid.

What is referred to herein as the "simulated gastric fluid" has the following composition, the pH of which can be made less than 3.0 by adjusting the amount of hydrochloric acid therein:

NaCl	-	1.4 grams
KCl	-	0.5 "
$CaCl_2$	-	0.06 "
Pepsin	-	3.2 "
HCl Distilled water	-	Suitable amounts
Total amount	-	1000 ml.

On the other hand, what is referred to as the "simulated intestinal fluid" has the following composition, the pH of which can be made 5.0—8.0 by adjusting the amount of sodium bicarbonate:

$NaHCO_3$	-	Suitable amount
Pancreatin	-	2.8 grams
Distilled water	-	Suitable amount
Total amount	-	1000 ml.

Substances suitable as the enteric coating material are, for example, sodium alginate, potassium alginate, ammonium alginate, cellulose acetate phthalate, sodium cellulose acetate phthalate, potassium cellulose acetate phthalate, ammonium cellulose acetate phthalate, cellulose acetate maleate, sodium cellulose acetate maleate, potassium cellulose acetate maleate, ammonium cellulose acetate maleate, polyvinyl alcohol phthalate, sodium polyvinyl alcohol phthalate, potassium polyvinyl alcohol phthalate, ammonium polyvinyl alcohol phthalate, polyvinyl alcohol maleate, sodium polyvinyl alcohol maleate, potassium polyvinyl alcohol maleate and ammonium polyvinyl alcohol maleate. The water-soluble salts of alginic acid such as sodium alginate, potassium alginate and ammonium alginate are particularly suitable, especially those salts whose absolute viscosity in a 1% aqueous solution at 20° C. is below 500 cp. Where rapid dissolution in the intestine is desired, the low viscosity is particularly valuable. However, usually a viscosity of from 60 to 100 cp. is suitable, the thickness of the coating having hardly any effect on its solubility in the intestine.

Coatings of water-soluble salts of alginic acid, like other enteric coating materials, are somewhat permeable, and thus considerable diffusion of the dextran sulphate salt can occur. This difficulty can be overcome by applying to the enteric coating a solution of acetoglyceride (an acetylated product of a glyceride of an aliphatic acid, the carbon atoms of the fatty acid being from 12 to 20) and an innocuous waxy substance such as beeswax, Carnauba wax, vegetable wax, Ibota wax or a synthetic wax, dissolved in an organic solvent.

The thickness of the coating layer of the enteric coating material is suitably from 0.05 to 1.0, particularly about 0.1—0.5 mm. In view of the fact that the water-soluble salts of dextran sulphate are highly unstable in the stomach and that their activity is reduced by the action of moisture, it is particularly desired that the coating layer be uniform over the tablet. If the tablets are made by the method consisting of applying a solution of the coating material in an organic solvent, there is a risk that the coating will tend to become uneven due to the intense agglutinating that can occur during the volatilisation of the solvent. If the coating is made thicker to prevent this, there is a risk that the disintegration of the tablet in the intestine will be hampered.

The preferred method of preparing the tablets comprises moulding or compressing a water-soluble salt of dextran sulphate to form an uncoated tablet, and coating said tablet uniformly with an enteric coating material which is insoluble in simulated gastric fluid (as hereinbefore defined) having a pH below 3.0 but dissolves or disintegrates in simulated

intestinal fluid (as hereinbefore defined) having a pH from 5.0 to 8.0.

The enteric coating can, for instance, be applied as follows. After applying a sealing and subcoating to the surface of the uncoated dextran sulphate tablets, an aqueous solution of adhesive, for instance gelatin, gum arabic or sugar is applied to the tablet surface so as to moisten it uniformly. When this coating has partially dried and has become tacky the coating material, for instance a powdered water-soluble salt of alginic acid, is applied. If necessary, the application of the adhesive and powder can be repeated several times to form a coating of the desired thickness.

In preparing the enteric-coated tablets of this invention, there are preferably added to the dextran sulphate salt diluent bases and lubricants such as starch, lactose, glucose, dextrin and talc and the mixture is formed into uncoated tablets by conventional moulding or compressing. Then after applying to the tablets a sealing and subcoating, they are coated evenly with the enteric coating material. Then, as described above, the outside of the tablets can be coated with acetoglyceride and a waxy substance.

When tablets containing sodium dextran sulphate (having an intrinsic viscosity of 0.02—0.05 in a 0.7 mol saline at 25° C. and a sulphur content of 13.0% by weight or more) were made into tablets according to the method of the invention and tested, they showed good lipolytic activity, and moreover in case of proper dosage did not cause a prolongation of the blood coagulating time.

The tablets of this invention have been tested *in vitro*, by the test described in the 6th Edition of the Japanese Pharmacopoeia. The results were that no abnormalities such as the excoriation or damage of the coating in a simulated gastric fluid were observed. On the other hand, in a simulated intestinal fluid the preparation disintegrated in 10 to 60 minutes. In the test of the simulated gastric fluid by the matachromasy reaction using Toluidine Blue, the result was negative, at least for a period of 2 hours.

In vivo tests were made in which four normal dogs weighing from 7 to 10 kg. were used, and when in fast the tablets made according to the present invention were orally administered in amounts corresponding to 10 mg., 20 mg., 30 mg. and 75 mg. of dextran sulphate per 1 kg. of body weight. Then every two hours blood was let, and by investigating the changes with the lapse of time in the blood coagulating time and lipolytic activity at the respective dosages the effectiveness of the enteric coating was judged. From these results it was observed that while the administration in terms of dextran sulphate (having an intrinsic viscosity in a 0.7 ml saline at 25° C. or 0.03 and a sulphur content of 18.0%) of 10—30 mg. showed hardly any prolongation of the blood coagulating time, the administration of 75 mg. showed a definite prolongation. On the other hand, the lipolytic activity was unmistakable in all cases.

As regards the methods of measurement, the blood coagulating time was by Lee White's method, while the lipolytic activity was measured by the ability of the so-called active plasma containing lipoprotein-lipase which is the lipemia clearing factor, set up in the blood by orally administering the tablets to clear the emulsion of below-described composition in a test tube. Namely, every 2 hours after administration blood was let by means of a syringe into which was introduced 0.2 cc. of a 10% sodium citrate solution, after which this was centrifuged for 5 minutes to separate the plasma. One cc. of this was added to 10 cc. of 1/15M phosphoric acid buffer solution (pH 7.4) together with 2 drops of a 20% sesame oil emulsion, to which was then mixed 25 cc. of human plasma (dried normal human plasma). After mixing this with 2 cc. of an emulsion incubated for 1 hour at 37° C., the turbidity was measured at 630—650 mμ using a photoelectric colourimeter, this measurement being called "A". Next, after incubating this mixture for 2 hours at 37° C., it was again measured in the same manner for its turbidity, this measurement being called "B". The decrease in turbidity, i.e., A—B (represented in $-\log T$) represents the lipolytic activity.

On the other hand, when tablets of dextran sulphate not provided with enteric coatings were administered orally to a normal dog such that the dosage was 75 mg./kg. in terms of dextran sulphate and the extent of absorption was tested, neither a prolongation of the blood coagulating time nor lipolytic activity was observed. Further, from the results of tests made by administering dextran sulphate tablets of this invention to humans, it was found that, depending upon the amount administered, lipolytic activity could be obtained without prolonging the blood coagulation time.

The invention is illustrated by the following Examples.

EXAMPLE 1

To 600 grams of a powdered sodium salt of dextran sulphate (intrinsic viscosity 0.025, sulphur content 16.5%) was added 432 grams of starch and 120 grams of lactose and the mixture was thoroughly mixed. Then, for the purpose of assisting dispersion of the dextran sulphate in the intestine and for promoting its absorption into the body system from the intestine, a solution of 12 grams each of the stearic acid ester of a polyoxyethylene and isopropyl myristate dissolved in 100 grams of anhydrous ethyl alcohol was added and thoroughly mixed. Next, a suitable amount of anhydrous ethyl alcohol was added to the

above mixture, after which the mixture was granulated.

After being air-dried at room temperature, 24 grams of talc was added as a lubricant, following which the mixture was made into tablets, each of 300 mg. 1000 Grams of the uncoated tablets thus obtained were placed in a coating pan, and after application of sealing and subcoating materials, 15 grams of the liquid adhesive composition of Formula I set out below was added so as to wet the tablets evenly. When the adhesive had partially dried and become tacky, 50 grams of sodium alginate powder (120 mesh, 60 cp.) was sprinkled over the tablets, and after rotating the pan for 5 minutes, warm dry air was blown in and the excess powder was removed while at the same time drying was accelerated.

After the enteric coating thus obtained had dried, the same liquid adhesive composition in increasing amounts of 30 grams and then 55 grams were used followed by sprinkling with further sodium alginate powder and drying the coating. This was then followed by adding in several installments 45 grams of the liquid composition of Formula 2 set out below and repeating the drying operations whereby the semi-permeable nature of the sodium alginate coating was overcome. Thereafter, smoothing and polishing operations were carried out according to known procedures, thereby obtaining the finished product.

The weight of the enteric-coated tablet prepared according to this method is 600 mg., its sodium alginate coating weighing an average of about 30—50 mg. These tablets showed no change in a simulated gastric fluid but disintegrated in about 10 minutes in a simulated intestinal fluid.

FORMULA 1

Gelatin	3	grams
Gum arabic	3	"
Sugar	28	"
Water	66	"
TOTAL	100	grams

FORMULA 2

Beeswax	10	grams
Acetylmonoglyceride	10	"
Carbon Tetrachloride	80	"
TOTAL	100	grams

When the enteric-coated tablets prepared according to this Example were orally administered to arteriosclerosis patients at the rate of 15 mg./kg. in terms of dextran sulphate and the total cholesterol, free cholesterol and c/p value were measured, the results in all cases showed a marked decrease. On the other hand, when the effects of this preparation on the blood coagulating time of healthy individuals were observed by orally administering these tablets continually over a 90-day period at the rate of 50 mg./kg. per day, the results showed no prolongation whatsoever of the blood coagulating time.

EXAMPLE 2

The procedure of Example 1 was repeated except that instead of sodium alginate a total of about 80 grams of sodium cellulose acetate phthalate was used.

The weight of the resultant enteric-coated tablets of dextran sulphate was 600 mg. and the thickness of its powder layer of sodium cellulose acetate phthalate was about 0.1 mm. These tablets showed no change in a simulated gastric fluid, but disintegrated in about 30 minutes in a simulated intestinal fluid. When this tablet was orally administered to arteriosclerosis patients, the results were practically the same as in the case of Example 1.

EXAMPLE 3

The procedure of Example 1 was repeated except that instead of sodium alginate about 150 grams of sodium polyvinyl alcohol phthalate was used.

The weight of the resultant enteric-coated tablet was 600 mg. and the thickness of its powder layer of sodium polyvinyl phthalate was about 0.2 mm. The results of the tests made of this tablet *in vitro* and *in vivo* were practically the same as in case of Example 1.

EXAMPLE 4

To 600 grams of powdered sodium salt of dextran sulphate ([η] 0.048, sulphur content 19.5%) were added 432 grams of starch and 120 grams of lactose and thoroughly mixed therewith. For the purpose of assisting dispersion of the dextran sulphate in the intestine and for promoting its absorption into the system from the intestine, a solution consisting of 12 grams each of the stearic acid ester of a polyoxyethylene and isopropyl myristate dissolved in 100 grams of anhydrous ethyl alcohol was added and thoroughly mixed. Next, a suitable amount of anhydrous ethyl alcohol was added to the above mixture, after which the mixture was granulated. After being air-dried at room temperature, 24 grams of talc was added as a lubricant, following which the mixture was made into tablets each of 300 mg.

1000 Grams of the uncoated tablets thus obtained were placed in a coating pan, and after the application of the known sealing and subcoating materials, warm air was blown in and the tablets heated to about 30° C. Then the liquid adhesive composition of Formula 3 set out below was applied to the tablets with a sprayer, and after the tablets dried the spraying was repeated. This operation was repeated several times and there-

after application of a smoothing coat and polishing were carried out according to known methods, thus obtaining the finished product.

The weight of the enteric-coated tablet prepared by this method was 600 mg. and the polyvinyl alcohol phthalate coating had a thickness of 0.05 mm. and a weight of about 2—3 mg. This tablet showed no change in a simulated gastric fluid but disintegrated in about 50 minutes in a simulated intestinal fluid.

FORMULA 3

Polyvinyl alcohol phthalate -	10 grams
A 50/50 alcohol/acetone mixture	90 „
TOTAL - - - - -	100 grams

In a test of the enteric-coated tablets, prepared by this Example *in vivo* at a dosage in terms of dextran sulphate of 30 mg./kg., a significant prolongation of the blood coagulating time was observed.

WHAT WE CLAIM IS:—

1. A tablet of a water-soluble salt of dextran sulphate having a uniform coating of an enteric coating material, said coating being insoluble in simulated gastric fluid (as hereinbefore defined) of a pH less than 3.0 but which dissolves or disintegrates in a simulated intestinal fluid (as hereinbefore defined) of a pH from 5.0 to 8.0.

2. A tablet according to claim 1, in which said enteric coating material comprises sodium alginate, potassium alginate, ammonium alginate, cellulose acetate phthalate, sodium cellulose acetate phthalate, potassium cellulose acetate phthalate, ammonium cellulose acetate phthalate, cellulose acetate maleate, sodium cellulose acetate maleate, potassium cellulose acetate maleate, ammonium cellulose acetate maleate, polyvinyl alcohol phthalate, sodium polyvinyl alcohol phthalate, potassium polyvinyl alcohol phthalate, ammonium polyvinyl alcohol phthalate, polyvinyl alcohol maleate, sodium polyvinyl alcohol maleate, potassium polyvinyl alcohol maleate or ammonium polyvinyl alcohol maleate.

3. A tablet according to claim 1 or 2, in which the thickness of the layer of said enteric coating material is 0.05—1.0 mm.

4. A tablet according to claim 3, in which the said thickness is 0.1—0.5 mm.

5. A tablet according to any of the preceding claims, in which the salt of dextran sulphate is the sodium or potassium salt.

6. A tablet of a water-soluble salt of dextran sulphate having an enteric coating, substantially as described herein.

7. A method of preparing enteric-coated tablets of a water-soluble salt of dextran sulphate, which comprises moulding or compressing a water-soluble salt of dextran sulphate to form an uncoated tablet, and coating said tablet uniformly with an enteric coating material which is insoluble in simulated gastric fluid (as hereinbefore defined) having a pH below 3.0 but dissolves or disintegrates in simulated intestinal fluid (as hereinbefore defined) having a pH from 5.0 to 8.0.

8. A method according to claim 7, in which said enteric coating material comprises sodium alginate, potassium alginate, ammonium alginate, cellulose acetate phthalate, sodium cellulose acetate phthalate, potassium cellulose acetate phthalate, ammonium cellulose acetate phthalate, cellulose acetate maleate, sodium cellulose acetate maleate, potassium cellulose acetate maleate, ammonium cellulose acetate maleate, polyvinyl alcohol phthalate, sodium polyvinyl alcohol phthalate, potassium polyvinyl alcohol phthalate, ammonium polyvinyl alcohol phthalate, polyvinyl alcohol maleate, sodium polyvinyl alcohol maleate, potassium polyvinyl alcohol maleate or ammonium polyvinyl alcohol maleate.

9. A method according to claim 7 or 8, in which the said coating material is applied as a powder to the uncoated tablet after the latter has been treated with a liquid adhesive.

10. A method according to claim 9, in which the sequence of the application of the adhesive and the powder is repeated in order to increase the thickness of the enteric coating.

11. A method of preparing enteric coated tablets of a water-soluble salt of dextran sulphate, substantially as described herein.

12. A method of preparing enteric coated tablets of a water-soluble salt of dextran sulphate, substantially as described in any of the Examples.

13. Enteric-coated tablets of a water-soluble salt of dextran sulphate when obtained by the method of any of claims 7—12.

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